REMARKS

Claims 1-18, 27, and 28 are pending in the application. Claims 1, 2, 8, 10, 13-18, 27, and 28 are withdrawn as being drawn to non-elected inventions. Applicants reserve the right to prosecute the non-elected claims in subsequent divisional applications. Claims 3-7, 9, 11, and 12 are currently being examined on the merits. Applicants thank the Examiner for acknowledging that method claims 13-15, 27, and 28 with the same scope will be rejoined upon allowance of the product claims.

Claims 3, 4, 5, 9, 11, and 12 have been amended to correct the dependence upon non-elected claims and to clarify the subject of the claimed invention. No new matter is added by these amendments. Entry of these amendments is respectfully requested.

Specification:

The Examiner required that the first line of the specification be updated to indicate that application 09/088,435 is now U.S. Patent 6,277,619. The specification has been amended herein to update this line.

Objections:

Claims 3-7 and 9 are objected to as being dependent upon non-elected claims. As amended herein, claim 3-7 and 9 are no longer dependent upon non-elected claims. Withdrawal of the objections to the claims is therefore respectfully requested.

Utility rejections under 35 U.S.C. §§ 101 and 112, first paragraph:

Claims 3-7, 9, 11, and 12 are rejected under 35 U.S.C. §§ 101 and 112, first paragraph, as allegedly not being supported by either a specific and substantial asserted utility or a well established utility. The rejection of the claims is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well-known to one of ordinary skill in the art.

The invention at issue are polynucleotides that encode a human serine dehydratase homolog, abbreviated as SDHH. The novel polypeptide is demonstrated in the specification to be a member of the class of serine dehydratase (SDH) proteins, enzymes involved in gluconeogenesis, the formation of

glucose, the primary fuel for cellular processes, from amino acids and certain types of fat (specification, p. 1). SDH is synthesized primarily in the liver. The specification discloses that serine dehydratase levels are decreased in human colon carcinoma and rat sarcoma, and altered serine dehydratase levels are associated with metabolic disorders such as liver tissue impairments, obesity, and diabetes (specification, pp. 2-3). Northern analysis shows the expression of SDHH in various libraries, 48% of which are cancerous, 29% are involved in immune response, and 23% are fetal, cell line, or proliferating (specification, p. 15, lines 20-22). As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, disease diagnosis, and as a serine dehydratase enzyme, none of which require knowledge of how the polypeptide encoded by the claimed polynucleotide actually functions physiologically.

The similarity of the polypeptide encoded by the claimed polynucleotides to other polypeptides of known, undisputed utility by itself demonstrates utility beyond the reasonable probability required by law. SDHH is, in that regard, homologous to rat liver serine dehydratase (GI 57225) and human liver serine dehydratase (GI 338030). In particular, SDHH and rat liver serine dehydratase share 53.2% identity, and SDHH and human liver serine dehydratase share 56.7% identity (specification, p. 15, lines 15-18). In addition, SDHH has the serine/threonine dehydratase pyridoxal-phosphate attachment site at E39 (specification, p. 15, lines 14-15).

This is more than enough homology to demonstrate a reasonable probability that the utility of the serine dehydratase enzyme family can be imputed to the claimed invention. It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small (Brenner, S.E., Chothia, C., and Hubbard, T.J.P., Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships, Proc. Natl. Acad. Sci. 95:6073-78 (1998), reference enclosed). Given homology in excess of 40% over 329 amino acid residues, the probability that the polypeptide encoded by the claimed polynucleotides is a member of the serine dehydratase enzyme family is, accordingly, very high.

The fact that the polypeptide encoded by the claimed polynucleotide is a member of the serine dehydratase protein family alone demonstrates utility. Each of the members of this class, regardless of their particular functions, are useful. There is no evidence that any member of this class of

polypeptides, let alone a substantial number of them, would not have some patentable utility. It follows that there is a more than substantial likelihood that the claimed polynucleotide also has patentable utility, regardless of the actual function of the polypeptide it encodes. The law has never required a patentee to prove more.

I. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. *See Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression"

such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

II. The Patent Examiner Failed to Demonstrate That a Person of Ordinary Skill in the Art Would Reasonably Doubt the Utility of the Claimed Invention

A. The membership of the polypeptide encoded by the claimed polynucleotides in the serine dehydratase enzyme family demonstrates utility

The biological functions of serine dehydratase (SDH) enzymes include gluconeogenesis, the formation of glucose, the primary fuel for cellular processes, from amino acids and certain types of fat (specification, p. 1, lines 7-14). The specification discloses that SDH levels are decreased in human

colon carcinoma and rat sarcoma (specification, p. 3, lines 1-5). In addition, altered serine dehydratase levels are associated with metabolic disorders such as liver tissue impairments, obesity, and diabetes. SDH is elevated in nephrectomized rats, and SDH mRNA levels are markedly increased in streptozocin-induced diabetes, while obese Zucker rats show significantly depressed SDH activity (specification, p. 2, lines 18-31). SDHH also possesses a very specific enzymatic activity, serine dehydratase activity. As such, the claimed invention has numerous practical, beneficial uses in drug development, toxicology testing, disease diagnosis, and as a serine dehydratase enzyme.

With respect to the asserted utilities of the claimed polynucleotides that encode SDHH, a protein that has utility as an SDH enzyme, the Examiner asserts that "[t]he assertion that the disclosed polypeptides have biological activities similar to serine dehydratase enzymes is not credible in the absence of supporting evidence" because of alleged difficulties in predicting protein function based on sequence homology (Office Action, pp. 6-9).

The Examiner does not (and cannot) assert either that the (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion, which are the requirements for establishing a *prima facie* case of lack of utility under the USPTO's standards (M.P.E.P. § 2017.01, III B). The mere allegation that Applicants' assertion that their claimed invention has a similar utility to the prior art polypeptide "might" be wrong (which is not established with any credibility by the Examiner in any case) does not rise to the level of establishing that Applicants' assertion is either fundamentally flawed or inconsistent with scientific logic. The Examiner has thus failed to meet his burden set forth at M.P.E.P § 2164.01(a) and by the C.C.P.A in *In re Marzocchi* (cited subsequently with favor many times by both the C.A.F.C. and by this Board) of presenting a proper *prima facie* case of lack of utility and enablement on these grounds, and this rejection must be reversed on this fact alone.

The Examiner's mere expression of doubt regarding the reliability of homology-based assignment of function (and thus use) is insufficient to support the necessary conclusion that one of ordinary skill in the art, reading Applicants' specification and claims together with any evidence or sound scientific reasoning supplied by the Examiner, would doubt the veracity of Applicants' asserted use, i.e., that the skilled worker would find it more likely than not that the asserted utility and enabling

disclosure was wrong and inoperable. It is only if that initial burden belonging to the Examiner is met that the burden of proof of utility and enablement shifts to the Applicants.

B. The use of sequence homology to predict protein function is well-known and accepted in the art

In any case, the "evidence" proffered by the Examiner to support his contention that the skilled worker would doubt the veracity of Applicants' asserted use(s) is inadequate to meet this initial burden.

The Examiner cites numerous references in order to assert two points, the first of which is that "the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities" (Office Action, p. 6). These references fail to provide support for the Examiner's position, as explained in detail below.

The Examiner cites Tischer et al. and Benjamin et al. as disclosing that VEGF and PDGF have opposite mitogenic activities. Applicants respectfully point out that the sequence homology between VEGF and the PDGF A and B chains is quite low, with little more than the conserved cysteine residues being conserved between the sequences (see Figures 4A, 4B, and 7 of Tischer). The homology is far less than the 52-56% identity for SDHH and its closest homologs. That VEGF and PDGF do not share the same function is therefore hardly surprising, and does not in any way imply that SDHH, with far greater homology to human and rat SDH, would not share the function of these proteins.

The Examiner cites Massague and Vukicevic et al. as disclosing that related members of the TGF family of proteins have different functions. Applicants note that the different members of the TGF family have from 22-70% sequence identity (and that the most closely related members are subunits of the same heterodimeric protein, not separate proteins with different functions) (Massague, p. 437, col. 1; and Figure 1). In most cases, therefore, the homology between TGF superfamily members is less than that observed between SDHH and rat liver SDH and human liver SDH (53.2% and 56.7% identity respectively, see the specification at p. 15, lines 17-18). These references disclosing differing functions in family members less closely related in sequence than SDHH and rat and human liver SDH, and spanning an entire superfamily of proteins, would not serve to make one of ordinary skill in the art

reasonably doubt that SDHH would have similar functions to the more closely related rat and human liver SDH.

The Examiner cites Pilbeam as allegedly disclosing two structurally closely related proteins, PTH and PTHrP, which can have opposite effects on bone resorption. The Examiner fails to notice that "[t]here is strong homology of PTHrP with PTH only in the amino-terminal domain" (Pilbeam, p. 717, col. 2) and that N-terminal fragments of both proteins in fact have similar biological activities (Pilbeam, p. 717, col. 2). It is only when the non-homologous C-terminal regions are added that the different activities emerge. Thus this reference supports Applicants' arguments that homologous protein sequences have similar functions.

The Examiner cites Kopchick et al. as disclosing antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid. Applicants respectfully point out that these mutants all involve substitutions of a specific amino acid that was conserved in all species studied, from fish to humans (Kopchick, p. 7, lines 5-8). This residue was also identified as essential for function based on structural analysis showing a cleft at that point in the structure, which was eliminated by substitutions with larger amino acids (Kopchick, p. 9, lines 21-34). The effects of a mutation deliberately engineered so as to alter an essential functional residue are irrelevant to the question of whether a naturally-occurring sequence retains the function of its homolog, as is the case here.

The Examiner also cites various references to support the second assertion underlying the rejection, that "function cannot be predicted based solely upon similarity to a protein found in the sequence databases" (Office Action, p. 7). For example, the Examiner cites Skolnick et al. as allegedly demonstrating that knowing the protein structure by itself is insufficient to annotate a number of functional classes. However, Skolnick et al. disclose that there are only 30-50% of proteins whose function cannot be assigned by any current methods (p. 37, col. 2). This makes it more likely than not that the polypeptide encoded by the claimed polynucleotides, which is homologous to members of a known and well characterized functional family, the serine dehydratase enzymes, is among the group which can be properly annotated.

Furthermore, Skolnick et al. disclose that "enzyme active sites are indeed more highly conserved than other parts of the protein" (p. 35, col. 1). SDHH contains the serine/threonine dehydratase pyridoxal-phosphate attachment site beginning at residue E39 (specification, p. 15, lines 14-15). As disclosed in the specification (p. 1, lines 15-17) and in Noda, C., Ito, K, Nakamura, T., Ichihara, A., Primary structure of rat liver serine dehydratase deduced from the cDNA sequence, FEBS Lett. 234:331-335 (1988) (reference enclosed), this site is highly conserved among serine and threonine dehydratases, although it differs from pyridoxal-phosphate attachment sites found in other pyridoxal phosphate dependent enzymes (Noda, p. 334; Figure 3). The heptapeptide GSFKIRG found in rat SDH is completely conserved in SDHH (residues G45-G51 of SEQ ID NO:1). In addition, serine and threonine dehydratases have another highly conserved domain of 14 residues beginning at I163 of human SDH, which is thought to be the active site for the dehydration reaction in conjunction with the pyridoxal-phosphate attachment site (Noda, p. 334, col. 2, and Figure 3). This region is also well conserved in SDHH (see L169-V182 of SEQ ID NO:1). The conservation of both these known sites would lead one of skill in the art to consider it highly probable that SDHH possesses SDH enzyme activity.

The Examiner cites Bork and Doerks et al. as stating that the error rate of functional annotation in the sequence database is considerable, making it difficult to infer correct function by comparison to sequences in the databases as errors are copied and propagated. To reinforce this point the Examiner also cites Bork et al., to the effect that "questionable interpretations are written into the sequence database and are then considered facts" (Office Action, p. 8). Applicants note that these references (as well as the others cited) pertain to automated sequence annotation by "software robots". (See, for example, Doerks et al. p. 248, col. 1; Bork p. 398, col. 1; and Bork et al. p. 426, col 1; as well as Smith et al., p. 1222, col. 1; and Brenner, p. 132, col. 1).

This issue is not relevant to the case here, since the protein encoded by the claimed polynucleotides was not assigned an annotation by a computer, but subjected to analysis by trained scientists who noted not only the homology to known SDH enzymes but also the conservation of the serine/threonine dehydratase pyridoxal phosphate attachment site. Unlike the examples in Bork et al., where software robots assigned functions based upon structural similarity of only a small domain of the

new protein to a small domain of a known protein, SDHH is homologous to rat and human liver SDH over the full length of the sequences. Moreover, SDHH was identified as a homolog of rat SDH, a protein that is known, on the basis of laboratory experimentation, to possess SDH enzyme activity and that has a known association of altered expression levels with human colon carcinoma and rat sarcoma, and with metabolic disorders such as liver tissue impairments, obesity, and diabetes (specification, p. 2, lines 18-31, and p. 3, lines1-5). Thus the issue of database errors does not arise here, since the homolog was annotated based upon direct experimental evidence, not homology to other proteins in the database. Indeed, it is acknowledged in the art that automated sequence prediction is an attempt to replicate what have been "successful approaches used by many researchers to assign probable functions to new sequences when previously studied and recognizable homologs exist" (Smith p. 1222, col.1; emphasis added). Such is the case here, and thus one of ordinary skill in the art would recognize the assignment of SDHH as having SDH enzyme activity and an association with cancer and metabolic disorders as most likely being correct.

Doerks et al. also discusses pitfalls in protein annotation such as misleading sequence similarities to regions that are not the active site, or failure to conserve active site residues. These considerations do not apply in the instant case, as SDHH is identified as an SDH enzyme not only by homology to a known SDH enzyme (rather than to incorrectly annotated unknown proteins, as was the case for one of the examples in Doerks et al., page 248, col. 3) but also by characteristic conserved domains found in all SDH enzymes. Nor has the Examiner provided any evidence that SDHH shares significant homology with proteins that are not SDH enzymes (parallel to the example in Doerks et al. in which a single sequence had homology to multiple hits from different protein families, shown on page 249).

The Examiner cites Smith et al. as arguing that there are numerous cases in which proteins of different functions share structural similarity due to evolution from a common ancestor. Applicants note that the only example provided is that of the transducin homologs, which share common WD repeat regions (Smith et al. p. 1222, col. 3), but not necessarily any large amount of overall homology, as is the case for SDHH and rat and human liver SDH.

The Examiner also cites Brenner et al. to argue that since there are only about 1000 major gene superfamilies in nature, most homologs must have different molecular and cellular functions. Again, this

is a generality that does not apply in the instant case, since the protein encoded by the claimed polynucleotides has been identified with much greater specificity than merely as a member of a "superfamily". The SDHH protein has been identified not simply as a pyridoxal-phosphate dependent enzyme, a family which includes proteins such as serine transhydroxymethylase and the amino acid transminases (Noda, p. 234, col. 2), nor simply as a member of the serine/threonine dehydratase family, but as a serine dehydratase enzyme. This is a fine enough distinction to identify SDHH as having the specific function of its limited subfamily.

Finally, the Examiner cites Bowie et al., as stating that the determination of three-dimensional structure from primary amino acid sequence, and the subsequent inference of detailed aspects of function from structure is extremely complex and unlikely to be solved in the near future. Applicants first note that it is not necessary to determine a protein's three-dimensional structure in order to ascertain its function; there are many proteins of well-known functions whose structures have not yet been determined. Applicants also respectfully direct the Examiner's attention to Bowie et al. at page 1306, column 2, wherein the authors state that "proteins are surprisingly tolerant of amino acid substitutions," and that "at some positions, many different nonconservative substitutions were allowed." It is well-known in the art that natural selection tends to conserve those residues critical for protein structure and function during the course of evolution. This is why the study of a set of related sequences can indicate which residues are critical, since these are the ones which are conserved between sequences of different species (see Bowie et al., page 1306, and pages 1308-1309). Thus Bowie supports Applicants' assertions that significant sequence homology to known SDH enzymes coupled with the conservation of known active sites would lead one of skill in the art to conclude that SDHH is in fact an SDH enzyme.

In conclusion, none of the cited references serve to meet the burden of demonstrating that the skilled worker would find it more likely than not that the asserted utility for the claimed proteins as SDH homologs having SDH enzyme activity and an association with cancer and metabolic disorders was not correct.

In addition, it is noted that, according to recent conversations with supervisory personnel in Technology Center 1600 of the USPTO, this aspect of the argument regarding the credibility of homology-based assertion of function has been discredited.

In fact, at a recent Biotechnology Customer Partnership Meeting held at the USPTO on April17, 2001, in a talk by Senior Examiner James Martinell, it was emphasized that Applicant's assertion that his claimed protein "is a member of a family of proteins that already known based upon amino acid sequence homology" can be effective as an assertion of utility for the claimed sequence. According to Dr. Martinell, the proper question for the Examiner to ask, after searching the prior art for the claimed protein, is "Would one of skill in the art accept that the protein has been placed in the correct family of proteins as is asserted?" The "two" [sic: three] possible answers that can be deduced from this prior art search are, according to Dr. Martinell:

- The search does not reveal any **evidence** that the family attribution made in the application is either **incorrect or may be incorrect**
- The protein either **more likely belongs to a family other than that asserted** in the application or **likely does not belong to the family asserted** in the application
- The search shows that the attribution is likely correct

(From handouts of Dr. Martinell's slides distributed April 17, 2001; emphasis added)

It is clear from the above that the tactic taken by the Examiner in asserting the very slight possibility that ANY minor sequence change might have a dramatic effect on the function of the protein has been abandoned by the USPTO as a credible basis for a rejection under either the utility requirement of 35 U.S.C. § 101 or the enablement requirement of §112, first paragraph.

However, in any case, it is noted that the Examiner has failed to meet the above requirements now recognized by the USPTO. He has cited no evidence particular to the claimed protein, e.g., inconsistent findings deduced from his search, upon which to base any objection to the assignment of functional homology to the family of serine dehydratase enzymes. Indeed, there is no such evidence.

Moreover, it must be remembered, as set forth in the USPTO's own M.P.E.P., that in order to raise such doubt in the veracity of Applicants' assertion, the Examiner must establish either (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. The Examiner has accomplished neither of these minimum standards.

C. The use of proteins encoded by polynucleotides expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

In addition to the use of SDHH as a serine dehydratase, an enzyme with a specific activity, another well-known use for SDHH is in expression profiling.

In recent years, scientists have developed important techniques for toxicology testing, drug development, and disease diagnosis. Many of these techniques rely on expression profiling, in which the expression of numerous genes is compared in two or more samples. Genes or gene fragments known to be expressed, such as the invention at issue, are tools essential to any technology that uses expression profiling.

The technologies made possible by expression profiling and the DNA tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et. al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29:655-691 (July 1999) (reference enclosed):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs. (Rockett et al., page 656.)

To the same effect are several other scientific publications, including Emile F. Nuwaysir, et al., Microarrays and Toxicology: The Advent of Toxicogenomics, Molecular Carcinogenesis 24:153-159 (1999) (reference enclosed); and Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, Toxicology Letters 112-13:467-471 (2000) (reference enclosed).

The more genes that are available for use in toxicology testing, the more powerful the technique. Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See the enclosed email from the primary investigator

on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding, indicating that even the expression of carefully selected control genes can be altered. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

Expression profiling is disclosed in the specification at, for example, p. 36, line 29 through p. 37, line 6. In addition, the specification discloses that the claimed polynucleotides can be used in microarrays "to monitor the expression level of large numbers of genes simultaneously and to identify genetic variants, mutations, and polymorphisms. This information may be used to determine gene function, to understand the genetic basis of a disorder, to diagnose a disorder, and to develop and monitor the activities of therapeutic agents." (Specification, p. 38, lines 1-6). Thus one of skill in the art would clearly know how to make and use the claimed polynucleotides encoding SDHH in expression profiling, without any further experimentation.

The Examiner asserts that the specification "does not disclose a correlation between any specific disorder and an altered level or form of the claimed polynucleotides," and that the specification "does not predict whether the claimed polynucleotides would be overexpressed or underexpressed in a specific, diseased tissue compared to healthy tissue" (Office Action, p. 9).

The Examiner's attention is respectfully directed to the specification wherein it is disclosed that SDH levels are decreased in human colon carcinoma and rat sarcoma (specification, p. 3, lines 1-5). In addition, altered serine dehydratase levels are associated with metabolic disorders such as liver tissue impairments, obesity, and diabetes. SDH is elevated in nephrectomized rats, and SDH mRNA levels are markedly increased in streptozocin-induced diabetes, while obese Zucker rats show significantly depressed SDH activity (specification, p. 2, lines 18-31). Thus the specification clearly discloses a correlation between the expression of SDH enzymes (of which SDHH is one) with specific disorders, as well as indicating the expected direction of altered expression.

Applicants further note that any polynucleotide sequence can be used in expression profiling even without such specific disease association, for example, as a control to monitor the side effects of drugs targeted at other genes or proteins. Because SDHH an enzyme involved in the important cellular process of gluconeogenesis, one of skill in the art would understand that polynucleotides encoding

SDHH would be useful members of a microarray for toxicology testing in order to determine that drugs targeted at other genes or proteins did not, as a side effect, also disrupt this important cellular process.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be overturned regardless of their merit.

D. The use of SCAH-2 in toxicology testing, drug discovery, and disease diagnosis, and as a serine dehydratase enzyme are practical uses beyond mere study of the invention itself

The PTO's rejection of the claims is tantamount to a declaration that the use of an invention as a tool for research is not a "substantial" use. Because the PTO's rejection assumes a substantial overstatement of the law, and is incorrect in fact, it must be overturned.

There is no authority for the proposition that use as a tool for research is not a substantial utility. Indeed, the Patent Office itself has recognized that just because an invention is used in a research setting does not mean that it lacks utility (Section 2107.01 of the Manual of Patent Examining Procedure, under the heading I. Specific and Substantial Requirements, Research Tools):

> Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact 'useful' in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose specific utility requires further research to identify or reasonably confirm.

The PTO's actual practice has been, at least until the present, consistent with that approach. It has routinely issued patents for inventions whose only use is to facilitate research, such as DNA ligases, acknowledged by the PTO's Training Materials to be useful.

The subset of research uses that are not "substantial" utilities is limited. It consists only of those uses in which the claimed invention is to be an **object** of further study, thus merely inviting further research on the invention itself. This follows from *Brenner*, in which the U.S. Supreme Court held that

a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the Court held that a compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945. ("What Applicants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines.") Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other, additional beneficial use in research.

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed invention or its protein products. It is a tool, rather than an object, of research. The claimed invention has numerous other uses as a research tool, each of which alone is a "substantial utility". These include use of the claimed polynucleotide sequences and the polypeptides they encode in disease diagnosis, expression profiling, and drug discovery (specification, pp. 36-37, pp. 37-38, and p. 39, lines 10-27).

E. To the Extent the Rejection of the Patented Invention under 35 U.S.C. § 112, First Paragraph, Is Based on the Improper Rejection for Lack of Utility under 35 U.S.C. § 101, it Must Be Reversed.

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

Enablement rejections under 35 U.S.C. § 112, first paragraph:

Claims 3-7, 9, 11, and 12 are rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. The Examiner asserts that "[a] mere factor of similarity of the sequences does not predict the activity of the new protein and even a small difference between sequences could render substantial differences between the activities of the proteins" (Office Action, p. 12). Applicants have

discussed in great detail above, in the section pertaining to the utility rejections, how the art in fact recognizes the validity of using sequence homology to predict protein function.

The Examiner further asserts that the specification "also fails to teach how to use SDHH as diagnostic tools and therapeutic agents or as pharmaceutical agents" and asserts that "no correlation between SDHH and metabolic diseases or cancer has been established" (Office Action, p. 12). Again, Applicants respectfully point out that the specification discloses that SDH levels are decreased in human colon carcinoma and rat sarcoma (specification, p. 3, lines 1-5). In addition, altered serine dehydratase levels are associated with metabolic disorders such as liver tissue impairments, obesity, and diabetes. SDH is elevated in nephrectomized rats, and SDH mRNA levels are markedly increased in streptozocin-induced diabetes, while obese Zucker rats show significantly depressed SDH activity (specification, p. 2, lines 18-31). Thus the specification clearly discloses a correlation between the expression of SDH enzymes (of which SDHH is one) with specific cancers and metabolic disorders. Methods of using the claimed polynucleotides in diagnosis of cancers and metabolic disorders are disclosed in the specification (pp. 36-37), as well as methods of using the claimed polynucleotides in expression profiling (p. 36, line 29 through p. 37, line 6), and in microarrays to monitor the expression level of large numbers of genes simultaneously and to identify genetic variants, mutations, and polymorphisms (p. 38, lines 1-6). Thus one of ordinary skill in the art would know how to used the claimed polynucleotides encoding SDHH without any undue experimentation.

With respect to the claimed polynucleotides encoding variants of SEQ ID NO:1, the Examiner asserts that the specification fails to provide an activity for SEQ ID NO:1, and thus one skilled in the art would not be able to screen for active naturally occuring variants of SEQ ID NO:1. The Examiner further asserts that protein chemistry is highly unpredictable and that "even a single amino acid substitution ... will often dramatically affect the biological activity of the protein" (Office Action, p. 13).

Applicants respectfully point out that the claims are directed to polynucleotides, not polypeptides, and thus it is the functionality of the claimed polynucleotides, not the polypeptides encoded by them, that is relevant. For this reason the various references cited by the Examiner regarding the effects of single amino acid substitutions (Office Action, p. 13) are irrelevant. Members

of the claimed genus of variants may be useful even if they encode proteins that lack serine dehydratase activity.

For example, the variant polynucleotides could be used for the detection of sequences related to SDHH (see the specification at p. 35, lines 22-26) including SDHH variants that may be associated with disease states, such as the diseases listed in the specification at p. 36, lines 4-13). See the specification at, for example, pp. 36-37 for disclosure of how to use the claimed sequences in diagnostic assays. The variant polynucleotides could also be used in microarrays to identify genetic variants, mutations, and polymorphisms, and for disease diagnosis and development and testing of therapeutic agents (see the specification at, for example, p. 38, lines 1-6). Thus one of ordinary skill in the art would know how to used the claimed variants without any undue experimentation.

With respect to the claimed biologically active fragments, the Examiner asserts that "the specification does not teach specific regions in the protein which are responsible for its biological activity" (Office Action, p. 14). The Examiner's attention is respectfully directed to the specification at p. 1, lines 15-17, wherein the specification discloses that "[a] motif which interacts with SDH's pyridoxal 5'-phosphate cofactor in several B6 enzymes is considered characteristic of SDH. (Noda et al. 1988, FEBS Lett. 234:331-335)." SDHH contains the serine/threonine dehydratase pyridoxal-phosphate attachment site beginning at residue E39 (specification, p. 15, lines 14-15). In addition, serine and threonine dehydratases have another highly conserved domain of 14 residues beginning at I163 of human SDH, which is thought to be the active site for the dehydration reaction in conjunction with the pyridoxal-phosphate attachment site (Noda, p. 334, col. 2, and Figure 3). This region is also well conserved in SDHH. Furthermore, the specification provides an assay for measuring serine dehydratase activity of SDHH (p. 50, lines 4-19). Thus one of skill in the art would have ample guidance to the selection of biologically active fragments of SEQ ID NO:1. The skilled artisan would also understand how to use these fragments, for example in the drug screening methods disclosed in the specification at p. 39, lines 10-27).

With respect to the claimed polynucleotides encoding immunologically active fragments of SEQ ID NO:1, the Examiner asserts that "while one can make antibodies which recognize a fragment of SEQ ID NO:1, the antibody may not recognize the native structure and therefore, would not be useful

for methods such as detection of SEQ ID NO:1" (Office Action, p. 14). Applicants respectfully point out that the specification provides guidance for the selection of immunologically active fragments of SEQ ID NO:1, "such as those near the C-terminus or in hydrophilic regions" (specification, p. 51, lines 29-30). Thus one of skill in the art would be directed away from making antibodies to hydrophobic regions which would not be exposed on the surface of the native protein.

For at least the above reasons, one of skill in the art would understand how to make and use the claimed polynucleotides encoding variants and fragments of SEQ ID NO:1 as well as SEQ ID NO:1 itself without any undue experimentation, and withdrawal of the enablement rejections under 35 U.S.C. § 112, first paragraph, is therefore respectfully requested.

Rejections under 35 U.S.C. § 102:

Claims 11-12 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by either Iwahori et al. or Accession Number AA573827. Both Iwahori et al. discloses a polynucleotide comprising over 60 contiguous nucleotides of SEQ ID NO:2. The Examiner asserts that the complementary sequence is inherent to the Iwahori et al. sequence. Accession Number AA573827 discloses a polynucleotide sequence comprising over 60 contiguous nucleotides of the complement to SEQ ID NO:2.

Applicants first note that the reference sequences consist only of portions of SEQ ID NO:2 or its complement, and thus do not anticipate claim 11. In order to further clarify that the complementary sequences recited in claim 11 are the complements of the full sequences of SEQ ID NO:2 or variants thereof, claim 11 has been amended herein to recite polynucleotides that are "completely complementary" to the polynucleotides of 11(a) and 11(b). This amendment is made solely in order to further clarify the subject matter covered by the claim, and does not further limit the claim in any way.

Claim 12, as amended herein, recites "[a]n isolated polynucleotide comprising at least 60 contiguous nucleotides of a polynucleotide of claim 11, wherein said polynucleotide encodes a fragment of SEQ ID NO:1 having serine dehydratase activity." An assay for measuring the serine dehydratase activity of SDHH are disclosed in the specification at p. 50, lines 4-19. There is no evidence that either of the reference polynucleotides encodes a fragment of SEQ ID NO:1 having serine dehydratase

activity, and given that neither of these polynucleotides encodes the region of SEQ ID NO:1 containing the pyridoxal-phosphate binding site beginning at residue E39 (specification, p. 15, lines 14-15) it is not possible that the peptide encoded by either polynucleotide could have serine dehydratase activity. Thus neither of the references anticipates claim 12.

Withdrawal of the rejections of claims 11 and 12 under 35 U.S.C. § 102(b) is therefore respectfully requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney at (650) 855-0555.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,

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Date: October 29, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Paragraph(s) beginning at line 2 of page 1 has been amended as follows:

This application is a divisional application of U.S. application Serial Number 09/088,435 filed on June 1, 1998, issued August 21, 2001 as U.S. Patent No. 6,277,619, entitled SERINE DEHYDRATASE HOMOLOG, the contents all of which are hereby incorporated by reference.

IN THE CLAIMS:

Claims **3, 4, 5, 9, 11, and 12** have been amended as follows:

3. **(Once Amended.)** An isolated polynucleotide encoding a polypeptide [of claim 1] selected from the group consisting of:

a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1,

b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid of SEQ ID NO:1,

c) a biologically active fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, and

d) an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1.

4. **(Once Amended.)** An isolated polynucleotide of claim 3 encoding [a polypeptide of claim 2] the amino acid sequence of SEQ ID NO:1.

5. **(Once Amended.)** An isolated polynucleotide of claim 4 having [a] the polynucleotide sequence of SEQ ID NO:2.

9. **(Once Amended.)** A method of producing a polypeptide [of claim 1,] selected from the group consisting of:

a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1,

b) a polypeptide comprising a naturally occurring amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO:1,

c) a biologically active fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, and

d) an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, the method comprising:

[a)] i) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide, and said recombinant polynucleotide comprises a promoter sequence operably linked to a polynucleotide encoding said polypeptide, and

[b)] ii) recovering the polypeptide so expressed.

11. **(Once Amended.)** An isolated polynucleotide selected from the group consisting of:

a) a polynucleotide comprising the [a] polynucleotide sequence of SEQ ID NO:2,

b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to the [a] polynucleotide sequence of SEQ ID NO:2,

c) a polynucleotide completely complementary to a polynucleotide of a),

d) a polynucleotide completely complementary to a polynucleotide of b), and

e) an RNA equivalent of a)-d).

12. **(Once Amended.)** An isolated polynucleotide comprising at least 60 contiguous nucleotides of a polynucleotide of claim 11, wherein said polynucleotide encodes a fragment of SEQ ID NO:1 having serine dehydratase activity.